ATTENUATION OF A PULSATILE PRESSURE COMPONENT IN THE NEURAL ARC OF THE ARTERIAL BAROREFLEX

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Abstract- **A transfer function from baroreceptor pressure input to sympathetic nerve activity (SNA) shows high-pass characteristics in the frequency range from 0.01 to 1 Hz in anesthetized rabbits. The high-pass characteristics of the neural arc contribute to a quick and stable arterial pressure (AP) regulation. However, if the high-pass characteristics hold up to the frequency of heart rate (3-5 Hz), a pulsatile pressure component in AP would yield an extremely large amplitude of pulsatility in SNA. Such a large amplitude in SNA would hit the nonlinearities in baroreflex pathways, thereby disable the baroreflex regulation of AP. We hypothesized therefore that the transfer gain at the frequency of heart rate would be much smaller than that predicted from the high-pass characteristics of the neural arc. In anesthetized rabbits (n=6), we perturbed carotid sinus pressure (CSP) according to a binary white noise with a switching interval of 50 ms. The transfer function from CSP to cardiac SNA was then estimated in the range from 0.012 to 10 Hz. The neural arc transfer function showed high-pass characteristics in the frequencies below 0.7 Hz, while losing the transfer gain above the frequency at -20 dB/decade. A simulation study indicated that the attenuation of the pulsatile pressure component in the neural arc was effective to retain the reflex regulation of AP.**
Keywords- **transfer function, simulation**

I. INTRODUCTION

Estimation of transfer functions among cardiovascular variables is useful in providing insight into the mechanisms of cardiovascular regulation [1-6]. In a previous study, we decomposed the carotid sinus baroreflex system into the neural arc from carotid sinus pressure (CSP) to sympathetic nerve activity (SNA) and the peripheral arc from SNA to arterial pressure (AP) [1]. A transfer function analysis revealed that the neural arc approximates the first-order high-pass filter in the frequency range between 0.01 and 1 Hz. In contrast, the peripheral arc approximates the second-order low-pass filter in this frequency range. A numerical simulation indicated that the fast neural arc compensated for the slow peripheral arc to achieve a quick and stable AP regulation. This simulation result was obtained based on nonpulsatile AP [1]. However, if we made AP pulsatile (4-Hz sinusoid with peak-to-peak amplitude of 20 mmHg), the pulsatile pressure yield an extremely large amplitude of pusatility in SNA due to the high-pass characteristics of the neural arc. This phenomenon does not affect the resulting AP regulation as long as the baroreflex system linearly operates. However, there exist nonlinearities such as threshold and saturation in the native baroreflex system. Thus, if the pulsatile signal is in fact amplified by the high-pass characteristics of the neural arc, the large amplitude of SNA would hit the nonlinearities in the baroreflex pathways, thereby disable the baroreflex regulation of AP. We hypothesized therefore that the transfer gain of the neural arc would wane somewhere below the frequency of heart rate. To test the hypothesis, we estimated the neural arc transfer function from CSP to SNA in anesthetized rabbits extending the upper frequency limit of the analysis to 10 Hz.

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II. METHODS

Six Japanese white rabbits weighing 2.6 to 3.4 kg were anesthetized by intravenous injection (2 ml/kg) of a mixture of urethane (250 mg/ml) and α-chloralose (40 mg/ml), and mechanically ventilated with oxygen enriched room air. To eliminate the effects of baroreflexes from the cardiopulmonary region and aortic arch, the vagal nerves and aortic depressor nerves were sectioned bilaterally through a midline cervical incision. The carotid sinuses were isolated bilaterally from the rest of the systemic circulation. The right cardiac sympathetic nerve originating from the stellate ganglia was sectioned through a midline thoracotomy, and a pair of stainless steel wire electorodes (Bioflex wire AS633, Cooner Wire) were attached to the nerve to record efferent SNA. The preamplified nerve signal was band-pass filtered at 150-1000 Hz, and was then full-wave rectified and low-pass filtered with a cutoff frequency of 30 Hz. To estimate the transfer function from CSP to

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Abstract

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SNA, we perturbed CSP according to a binary white noise signal with a switching interval of 50 ms for 10 min, using a servo-controlled piston pump (model ET-126A, Labworks). The mean CSP was adjusted to the equilibrium pressure between CSP and AP. The peak-to-peak amplitude of CSP perturbation was set at 40 mmHg. CSP, SNA, and AP data were recorded at a sampling rate of 200 Hz and stored on a hard disk of a dedicated laboratory computer system.

In order to estimate the neural arc transfer function, we treated CSP as the input and SNA as the output of the system. We segmented the input-output data pairs into ten sets of 50% overlapping bins of 2^{14} data points each. For each segment, a linear trend was subtracted, and a Hanning window was applied. We then obtained frequency spectra of the input and output by a fast Fourier transform. We ensemble averaged the input power, $S_{CSP\cdot CSP}(f)$, output power, $S_{SNA\cdot SNA}(f)$, and crosspower between the input and output, $S_{SNA\cdot CSP}(f)$ over the ten segments. f represents frequency. Finally, we calculated the neural arc transfer function using the following equation [7].

$$H(f) = \frac{S_{SNA\cdot CSP}(f)}{S_{CSP\cdot CSP}(f)}$$

To quantify the linear dependence between the input and output, we calculated a magnitude-squared coherence function using the following equation [7].

$$Coh(f) = \frac{\left|S_{SNA\cdot CSP}(f)\right|^2}{S_{CSP\cdot CSP}(f)S_{SNA\cdot SNA}(f)}$$

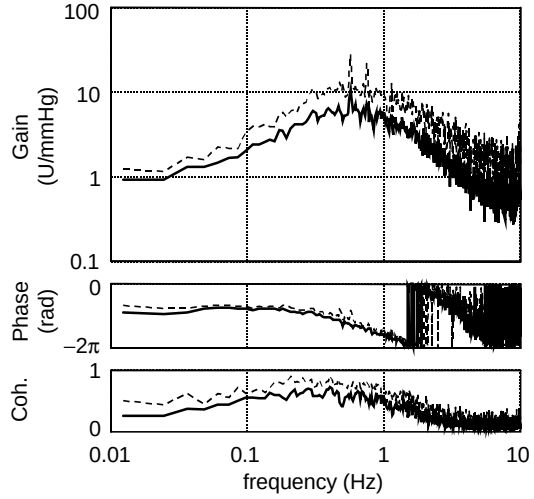

Fig. 1. Transfer function from carotid sinus pressure to sympathetic nerve activity. The solid and dashed lines indicate mean and mean+S.D. values.

IV. RESULTS

Figure 1 shows a transfer function from CSP to SNA averaged from all animals. The gain plot (*top*), phase plot (*middle*), and coherence function (*bottom*) are shown. The gain value increased as the frequency increased from 0.012 to 0.7 Hz. Above 0.8 Hz, however, the gain value decreased as the frequency increased. The gain value at 5 Hz was similar to that at 0.012 Hz, indicating that the pulsatile pressure component would not be enhanced in the neural arc of the arterial baroreflex. The phase value approximated $-\pi$ radians in the lowest frequencies, reflecting the negative feedback nature of the neural arc. The coherence values showed moderate linearity between CSP and SNA in the frequency range between 0.1 and 1 Hz. The coherence values were smaller in the frequencies below 0.1 Hz and above 1 Hz. The coherence values approached zero in the frequencies above 5 Hz.

V. DISCUSSION

Although the high-pass characteristics of the neural arc have been identified in our previous study [1], the transfer function of the neural arc around the frequency of heart rate (3-5H in rabbits) remained unknown. To our best knowledge, this is the first to reveal the neural arc transfer function beyond 1 Hz (Figure 1). The neural arc lost its transfer gain above 0.8 Hz in agreement with our hypothesis.

In order to elucidate the physiological meaning of the decreasing gain above 0.8 Hz seen in Figure 1, we constructed two types of simulators for the arterial baroreflex. One simulator (*SIM1*) has a neural arc with high-pass characteristics alone (Fig. 2A). The mathematical description of the neural arc for *SIM1* is as follows.

$$H_N(f) = \left(1 + \frac{f}{f_C}\,j\right)\exp(-2\pi fjL)$$

where f_C and L indicate the corner frequency (in Hz) of the high-pass filter and lag time (in s), respectively. f indicates the frequency (in Hz). j is the imaginary unit. We set f_C at 0.1 Hz and L at 0.5 s.

The other simulator (*SIM2*) has a neural arc that mimicked the native neural arc transfer function (Fig. 3A). The mathematical description of the neural arc for *SIM2* is as follows.

$$H_N(f) = \frac{\left(1 + \frac{f}{f_{C1}}\,j\right)}{\left(1 + \frac{f}{f_{C2}}\,j\right)^2}\exp(-2\pi fjL)$$

where f_{C1} indicates the corner frequency of the high-pass filter, and f_{C2} indicates the higher frequency limit above which the transfer gain decreases. We set f_{C1} and f_{C2} at 0.1 and 0.8 Hz, respectively.

For both *SIM1* and *SIM2*, the peripheral arc transfer function was modeled using a second-order low-pass filter with a lag time as follows [1].

$$H_P(f) = \frac{1}{\left[1 + 2? \frac{f}{f_N} j - \left(\frac{f}{f_N}\right)^2\right]} \exp(-2\mathrm{p} f j L)$$

where f_N and ζ indicate the natural frequency and damping rate, respectively. We set f_N and ζ at 0.07 Hz and 1.37, respectively. The lag time, L, was set at 1 s for the peripheral arc.

First, we simulated the closed-loop AP response against 40-mmHg stepwise pressure decrease using *SIM1* and *SIM2* without including any nonlinearities. The pulsatile pressure was simulated by a 4-Hz sinusoidal pressure variation with the peak-to-peak amplitude of 20 mmHg. As shown in Figures 2B and 3B, the exogenous perturbation was attenuated to -20 mmHg, on average, both in *SIM1* and *SIM2*. The time for the AP response to reach steady state was slightly shorter in *SIM1* than in *SIM2*, indicating that the high-pass characteristics beyond 1 Hz was effective to improve the quickness of the AP response against exogenous perturbation. However, at the frequency of 4 Hz, the input amplitude was enhanced as much as 40-folds that at 0.01 Hz in *SIM1*. Thus, the peripheral arc in *SIM1* was exposed to SNA changes comparable to the peak-to-peak input amplitude of 800 mmHg (20 mmHg×40). The native peripheral arc unlikely has the operating range wide enough to process this large signal.

Next, we put a nonlinear component with threshold and saturation in the course from the neural arc to the periphral arc components as a typical example. Because the magnitude of the AP response to static changes in SNA would be at most 200 mmHg centering around the operating pressure, we set the threshold and saturation by SNA values corresponding to the peak-to-peak input amplitude of 200 mmHg. This nonlinearity did not yield any deteriorating effects on the AP regulation in both *SIM1* and *SIM2* when nonpusatile AP was used for the simulation. However, when pulsatile AP was used for the simulation, the reflex regulation of AP against exogenous pressure perturbation was blunted in *SIM1* by the inclusion of the nonlinearity (Figure 2C). In contrast, the reflex regulation of AP against exogenous pressure perturbation was well preserved in *SIM2* even in the presence of the nonlinearity (Figure 3C). These simulation results indicate that the attenuation of the pulsatile component is effective to avoid the failure of AP regulation by the arterial baroreflex.

There are several limitations to the present study. First, we did not measure the nonlinearity of the peripheral arc between SNA and AP. However, the lowest and highest pressure values attained by baroreflex activation and deactivation were about 50 mmHg and 150 mmHg, respectively, in our experimental settings. Because we set the threshold and saturation of the nonlinearity based on SNA values corresponding to 100-mmHg below and 100-mmHg above the operating point, respectively, the linear range of our simulation would cover physiological linear range of the peripheral arc. Although our simulation settings less likely caused the nonlinear AP response than the native peripheral arc, the pulsatile pressure with peak-to-peak

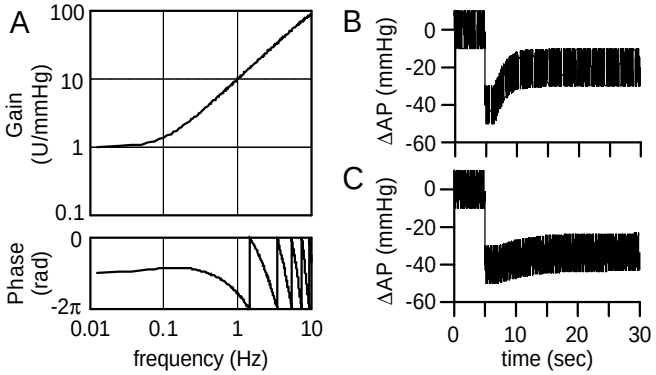

Fig. 2. A: The neural arc transfer function model with high-pass characteristics alone. B: A simulation result of arterial pressure (AP) response against stepwise pressure decrease obtained from a linear model. C: A simulation result of AP response against stepwise pressure decrease obtained from a model including nonlineaities with threshold and saturation.

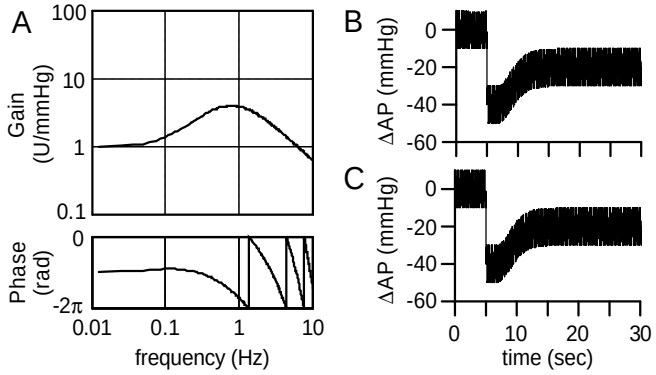

Fig. 3. A: The neural arc transfer function model mimicking changes in transfer gain of the native neural arc. B: A simulation result of arterial pressure (AP) response against stepwise pressure decrease obtained from a linear model. C: A simulation result of AP response against stepwise pressure decrease obtained from a model including nonlinearities with threshold and saturation.

amplitude of 20 mmHg still blunted the reflex regulation of AP in *SIM1*. Thus, we believe that the attenuation of the pulsatile pressure component plays an important role to retain the reflex regulation of AP in the native baroreflex system as well.

Second, there exists a species difference in the frequency of heart rate. Because the neural arc transfer function at the frequency of heart rate in other species remains unknown, the simulation results in the present study should be carefully interpreted.

VI. CONCLUSION

The neural arc of the baroreflex attenuates the pulsatile pressure component to retain the ability of reflex regulation of AP in rabbits. If the attenuation does not exist, the enhanced pulsatile pressure component would saturate the peripheral arc signal transduction, hampering the reflex regulation of AP against exogenous pressure perturbation.

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